Intellectual and motor performance, quality of life and psychosocial adjustment in children with cystinosis

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Abstract: Cystinosis is a rare multisystemic progressive disorder mandating lifelong medical treatment. Knowledge on the intellectual and motor functioning, health-related quality of life and psychosocial adjustment in children with cystinosis is limited. We have investigated nine patients (four after renal transplantation) at a median age of 9.7 years (range 5.3-19.9 years). Intellectual performance (IP) was analysed with the Wechsler Intelligence Scale for Children-III (seven children) and the Kaufman Assessment Battery for Children (two children). Motor performance (MP) was evaluated using the Zurich Neuromotor Assessment Test, and quality of life (QOL) was studied by means of the Netherlands Organization for Applied Scientific Research Academical Medical Center Child Quality of Life Questionnaire. Psychosocial adjustment was assessed by the Child Behavior Checklist. The overall intelligence quotient (IQ) of our patient cohort (median 92, range 71-105) was significantly lower than that of the healthy controls ($p = 0.04$), with two patients having an IQ < 85. Verbal IQ (93, range 76-118) was significantly higher than performance IQ (90, range 68-97; $p = 0.03$). The MP was significantly below the norm for pure motor, pegboard and static balance, as well as for movement quality. The patients' QOL was normal for six of seven dimensions (exception being positive emotions), whereas parents reported significant impairment in positive emotions, autonomy, social and cognitive functions. Significant disturbance was noted in terms of psychosocial adjustment. Based on the results from our small patient cohort, we conclude that intellectual and motor performance, health-related QOL and psychosocial adjustment are significantly impaired in children and adolescents with cystinosis.

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ORIGINAL ARTICLE

Intellectual and motor performance, quality of life and psychosocial adjustment in children with cystinosis

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Abstract Cystinosis is a rare multisystemic progressive disorder mandating lifelong medical treatment. Knowledge on the intellectual and motor functioning, health-related quality of life and psychosocial adjustment in children with cystinosis is limited. We have investigated nine patients (four after renal transplantation) at a median age of 9.7 years (range 5.3–19.9 years). Intellectual performance (IP) was analysed with the Wechsler Intelligence Scale for Children-III (seven children) and the Kaufman Assessment Battery for Children (two children). Motor performance (MP) was evaluated using the Zurich Neuromotor Assessment Test, and quality of life (QOL) was studied by means of the Netherlands Organization for Applied Scientific Research Academical Medical Center Child Quality of Life Questionnaire. Psychosocial adjustment was assessed by the Child Behavior Checklist. The overall intelligence quotient (IQ) of our patient cohort (median 92, range 71–105) was significantly lower than that of the healthy controls ($p=0.04$), with two patients having an IQ<85. Verbal IQ (93, range 76–118) was significantly higher than performance IQ (90, range 68–97; $p=0.03$). The MP was significantly below the norm for pure motor, pegboard and static balance, as well as for movement quality. The patients' QOL was normal for six of seven dimensions (exception being positive emotions), whereas parents reported significant impairment in positive emotions, autonomy, social and cognitive functions. Significant disturbance was noted in terms of psychosocial adjustment. Based on the results from our small patient cohort, we conclude that intellectual and motor performance, health-related QOL and psychosocial adjustment are significantly impaired in children and adolescents with cystinosis.

Keywords Cystinosis · Intellectual performance · Motor performance · Psychosocial adjustment · Quality of life

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Introduction

Cystinosis is a rare, multisystemic autosomal recessive disorder characterized by a defective lysosomal transport of cystine leading to intralysosomal cystine accumulation [1–7]. The disease is attributed to mutations in the *CTNS* gene encoding cystinosin [4]. Pathogenetic mechanisms include impaired mitochondrial function [8], defective Na^+-dependent cotransporters [9] and increased apoptosis rate [8, 10]. Cysteamine is the only therapeutic agent known

to be effective in depleting the intra-lysosomal accumulation of cystine, but endstage renal failure is still common during the second decade of life in many patients [1, 3].

Chronic renal disease has been associated with impairments in neurocognitive outcome and quality of life (QOL) [11, 12]. Limited information is available on adults with cystinosis in terms of intellectual performance (IP), motor performance (MP), QOL and psychosocial adjustment (PA). Children with cystinosis have been found to have of visual processing impairment [13], poor arithmetic performance [14] and mild intellectual deficits [15], but little is known on the MP, QOL and PA of children with this condition. However, children with chronic kidney diseases of various origins are at risk of impaired PA [16], externalizing behavioural problems and impaired QOL [12, 17–19]. We have previously reported neurocognitive outcome and QOL in those children using standardized and validated assessment tests and questionnaires [11, 12, 20].

The aim of this case series was to assess IP, MP, QOL and PA in nine children and adolescents with cystinosis. We also performed cerebral magnetic resonance imaging (MRI) to assess central nervous system (CNS) pathology (e.g. atrophy, calcifications, benign intracranial hypertension).

Patients and methods

Patients

Since 1970, 11 patients with cystinosis have been followed at the University Children's Hospital in Zurich. Two patients died since the initiation of the study: one within 24 h of renal transplantation (RTPL) due to acute heart failure, and the other succumbed to spinalioma 11 years after RTPL. Nine patients (four girls, five boys) from eight families were therefore included in this study, four of whom had had RTPL (Table 1).

Diagnosis was made based on cystine content in white blood cells. Medical treatment consisted of cysteamine (60 mg/kg per day given in four to five doses) in all patients; white blood cystine content was not measured routinely. Before RTPL, further medication included oral electrolytes, i.e. sodium, potassium, phosphorus and bicarbonate (all patients), 1,25-dihydroxycholecalciferol (all patients), L-thyroxine for hypothyrodism (patients B, C, F, I), recombinant erythropoietin (A, C, E) and human growth hormone (A, B, C). None of the patients were diagnosed with diabetes mellitus or with a significant visual impairment.

After RTPL, immunosuppression consisted of cyclosporine A (G, H, I; trough level 80–120 ng/ml) or tacrolimus (F; trough level 4–8 ng/ml), mycophenolate mofetile (G, H; daily dose of 1200 and 900 mg/m^2 body surface in patients on cyclosporine A and tacrolimus, respectively) or azathioprine (F, I; dose 1 mg/kg body weight). One patient (I) was on low-dose alternate-day prednisone (7.5 mg), and three patients (F, G, H) were off steroids. Patients G and I were on antihypertensive medication.

The following parameters were analysed: (1) casual blood pressure, measured in the sitting position targeting systolic blood pressure <95th percentile [21], (2) glomerular filtration rate (GFR, estimated by the Schwartz formula [22] with a *k*-factor of 40 based on comparison with creatinine (Cr)-EDTA clearance measurements), (3) audiometry, (4) body weight and body height and (5) body mass index (BMI).

One patient (I) had developed post-transplant lymphoproliferative disorder (PTLD) (B-non-Hodgkin lymphoma stage III) 2 years after RTPL; chemotherapy and reduction of immunosuppressive therapy resulted in long-term remission.

Seven children lived with both parents; the parents of patient H were divorced. Seven families were Swiss, and one family (D) was Portuguese.

Table 1 Clinical data

Patient/sex	Age at evaluation (years)	Age at diagnosis (years)	Age at RTPL/Type of donor (years)	GFR (ml/min per 1.73 m^2)
A/female	5.3	1.1	-	46
B/female[a]	5.7	0.1	-	85
C/female[a]	9.2	1.6	-	44
D/female[b]	9.3	4.3	-	64
E/male	9.7	1.8	-	20
F/male	11.8	1.8	7.1/LRD	61
G/male	13.3	3.8	9.4/LRD	83
H/male	15.8	1.1	13.5/LRD	56
I/male[c]	19.9	5.3	12.5/CD	31

RTPL, Renal transplantation; LRD, living related donor; CD, cadaveric donor; GFR, glomerular filtration rate (estimated by the Schwartz formula) [22]

[a] Siblings

[b] Nephropathic cystinosis and cystic fibrosis [35]

[c] Post-transplant lymphoproliferative disorder (PTLD)

Methods

Intellectual performance

The Wechsler Intelligence Scale for Children (WISC-III) [23, 24] was given to seven patients, all of school age (C–I). The WISC-III is used in children aged 6–16 years and is summarized in three intelligence quotient (IQ) scales, full scale (FSIQ), verbal (VIQ) and performance (PIQ), with a mean score of 100 and a standard deviation (SD) of 15. One young adult (I) was also tested with the WISC-III to obtain test results for comparison purposes.

Two children <6 years of age (A and B) were assessed with the German version of the Kaufman Assessment Battery for Children (K-ABC) [25, 26]. The K-ABC is used in preschool and school-aged children. It is composed of two scales, the mental processing composite and the achievement scale.

Motor performance

Motor performance was assessed with the Zurich Neuromotor Assessment (Z-NMA) [27, 28], a standardized testing procedure assessing timed MP and movement quality in children aged 5–18 years.

Eight of the nine children performed the motor test; one child did not cooperate sufficiently to obtain reliably timed results. Motor performance is divided into four timed components based on the complexity of the motor task (pure motor, pegboard, dynamic and static balance) and one component that assesses movement quality by measuring associated movements. We transformed the raw data into individual deviations from these age-adjusted normative values, which are expressed as standard deviations scores (SDS) [27, 28].

Cerebral MRI and spectroscopy

Magnetic resonance imaging was performed on eight patients using standard imaging protocols, including multiplanar T1-weighted spin-echo and T2-weighted fast spin-echo images covering the brain from the skull base to the vertex. It could not be performed on one child because of logistic problems. Diffusion-weighted MRI and ^{1}H magnetic resonance spectroscopy (MRS) results were available for four children. All images were obtained using a 1.5-Tesla MRI unit (General Electric Medical Systems, Milwaukee, WI) and were evaluated by two paediatric neuroradiologists. The ventricles and subarachnoid space were rated using an arbitrary scaling system as (1) normal, (2) mildly enlarged, (3) moderately enlarged or (4) significantly enlarged. In addition, the perivascular Virchow Robin spaces were evaluated and graded as either (1) normal or (2) prominent. Moreover, the cerebral white matter was evaluated for focal white matter lesions, the degree of white matter myelination (delayed, age appropriate or accelerated) and calcifications.

The TNO–AZL child quality of life questionnaire

The Netherlands Organization for Applied Scientific Research Academical Medical Center (TNO–AZL) Child Quality of Life Questionnaire (TACQOL) [29] comes in two forms, one for the parent and one for the child; both are designed to assess the QOL in children aged 8–15 years with chronic diseases. The questionnaire consists of seven scales assessing physical complaints (Body), cognitive (Cognition), social functioning (Social), autonomy (Auto), basic motor function (Motor), global positive emotional functioning (Emotion positive) and global negative emotional functioning (Emotion negative), and its questions focus on problems in these areas. The child's emotional response to the problem may also be assessed. The items are scored on scale of 4–0 (4 = problem never occurred; 3 = problem occurred, but child felt well; 2 = problem occurred, but child did not feel well; 1 = problem occurred, child felt rather badly; 0 = problem occurred, child felt badly). The maximum score for the first five domains is 32, while 16 is the maximum score for the emotional scales; the higher the score, the better the QOL.

Studies on normal control and clinical populations have confirmed the internal and external validity of the questionnaires [29, 30]. Normal values for the Child Form based on results obtained from more than 2300 healthy Dutch children aged 8–15 years (communicated by AGC Vogels, Sept 15, 2006). Reference values for the Parent Form were retrieved from the scale manual based on data from 1618 parents of healthy children aged 6–11 years [30].

Psychosocial adjustment

The Child Behavior Checklist (CBCL) is a standardized measure with excellent psychometric properties that enable a parent to report on a child's behavior [31]. It consists of 120 items assessing internalizing (withdrawn, somatic complaints, anxiety/depression, thought problems) and externalizing behaviour scales (social problems, attention problems, delinquent and aggressive behaviour). A total behavioural problem score is calculated from these problem scales, and this is compared with age- and sex-matched normative data (T-score). A higher score indicates greater child maladjustment. In this study, the German version of the CBCL was used; reference values are based on results obtained from 2865 healthy German children and adolescents [32, 33].

Procedure

The study was approved by the Ethical Committee of the University Children's Hospital of Zurich. Written informed consent was obtained from either the patient (aged >18 years), the parents or both. All nine patients tested for IP and MP were seen by the same paediatrician, who was not involved in the patient's care and unaware of current renal/graft function. The examiner was monitored by video recordings. German translations of all QOL and PA questionnaires followed published guidelines, including independent back-translation [34]. All patients >6 years were interviewed by the same investigator using the TACQOL–Child form. The TACQOL–Parent Form was completed by all parents separately. The forms were filled in either during the clinic visit in the hospital or at home. Seven children returned the TACQOL–Child form (A, B were too young), and eight parents returned the CBCL and TACQOL–Parent form.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software package, vers. 11.5 (SPSS, Chicago, IL.). A value of $p \leq 0.05$ was considered to be significant. Results were either presented as the mean and standard deviation (SD) or as the median and range. For comparison between groups, the Mann–Whitney–Wilcoxon U test was used; for comparison with norm values, the one-sample Wilcoxon signed ranks test (IP, MP) and Student's t test (QOL, PA) were applied. Correlation analysis was performed using the Spearman correlation.

Results

Clinical examination

Clinical data are summarized in Table 1. Patients were examined at a median age of 9.7 years (range 5.3–19.9 years). Two patients (G, I) required antihypertensive treatment when the blood pressure was <95th centile. Audiometry and neurological examination were normal in all patients. One patient (D) had concomitant, yet clinically mild cystic fibrosis [35], while another patient (I) had recovered from PTLD.

Intellectual and motor performance

The overall median full scale IQ was 92 (range 71–105), which was significantly lower than that of the normal controls (p=0.04). No child was diagnosed with mental retardation (IQ<70), however, two children (E, G) had IQ-scores <85 (i.e. mean >1 SD) of 71 and 75, respectively. With the exception of patient G, who was in a special school for mentally handicapped children, all children were in regular or nursery school. For those children examined with the WISC-III (C–I), the PIQ (median 90; range 68–97) was significantly lower than that of the normal controls (p=0.01) and also significantly lower than the VIQ (median 93, range 76–118, p=0.03) (Table 2).

The MP was significantly below the norm for all components except dynamic balance (Table 3). In the dynamic balance, the difference from the norm did not reach statistical significance (Wilcoxon signed ranks test p=0.08).

Quality of life questionnaire (TACQOL) and psychosocial adjustment

The patients' self-report of QOL was normal for six of the seven dimensions, with the exception being positive emotions, which were significantly impaired. The parents reported significant impairment in positive emotions, autonomy, social and cognitive functions (Table 4). The PA was significantly impaired, with higher scores on the internalizing, externalizing and total behavior scale of the CBCL (Table 5).

Magnetic resonance imaging and spectroscopy

The results are summarized in Table 2. Incidental focal findings included mesial sclerosis of the hippocampus in one patient (G) and developmental venous anomaly in another child (C). Four children were found to have mildly or moderately enlarged ventricles. The MRI findings were not related to IP or MP. Diffusion-weighted MRI and ^{1}H MRS did not show any additional pathology.

Discussion

Despite a growing understanding of the genetic, pathophysiological and therapeutic aspects of cystinosis [1–7, 36–38], only limited information is available on the long-term developmental and psychosocial outcome of this disease. This study provides further information on intellectual and motor performance (IP and MP), quality of life (QOL) and psychosocial adjustment (PA) in children and adolescents with cystinosis. The results of the standardized tests used in this study demonstrate that the IP, MP and PA of our patient cohort were significantly impaired. We also found that parents rated their children's QOL more pessimistically than the children themselves.

Intellectual performance—performance (non-verbal) IQ in particular—was affected. This finding is in line with those from other studies, indicating that a significant

Table 2 Intellectual performance, magnetic resonance imaging findings and schooling situation

Patient	Test	FSIQ	VIQ	PIQ	MRI	Schooling
A	K-ABC	97			Mildly enlarged ventricles	Nursery school
B	K-ABC	92			Normal	Nursery school
C	WISC-III	89	90	90	Normal	Regular school
D	WISC-III	92	93	91	No MRI available	Regular school
E	WISC-III	75	82	69	Normal	Regular school
F	WISC-III	100	104	97	Mildly enlarged ventricles widened subarachnoidal space	Regular school
G	WISC-III	71	76	68	Mesial temporal sclerosis	Special school
H	WISC-III	99	104	95	Moderately enlarged ventricles	Regular school
I	WISC-III	105	118	89	Moderately enlarged ventricles	Completed high school, apprenticeship
Median		92[a]	93	90[b]		

K-ABC, Kaufman Assessment Battery for Children; WISC-III, Wechsler Intelligence Scale for Children; FSIQ, full scale intelligence quotient (IQ); VIQ, verbal IQ; PIQ, performance IQ; MRI, magnetic resonance imaging

[a] $p=0.04$ (Wilcoxon signed ranks test compared to norm)

[b] $p=0.01$ (Wilcoxon signed ranks test compared to norm)

proportion (65%) of children with chronic kidney disease manifest developmental delay [17] and that performance IQ is more impaired than verbal IQ [17]. Focusing on patients with cystinosis, our results are in line with those of William et al. [15], who demonstrated a significantly lower IQ in 15 patients compared to controls, with the most significantly affected score being the item "spelling". Ballantyne et al. [14] evaluated academic achievement; these researchers found that the patients had lower average IQ ranges on both arithmetic (mean 89.95±13.77) and spelling skills (mean 90.68±18.81), while those for reading were higher (mean 97.47±15.59). Interestingly, all but one patient were in regular school. This may indicate that despite the lower IQ scores, the Swiss school system can accommodate these children by either providing individualized teaching or through an integration system where remedial schooling is integrated in the regular school class. Visual functioning has been extensively studied by Ballantyne et al. In one study [13] they found that children with cystinosis may manifest specific deficits in visuospatial functions. We did not examine these specific functions; however, some subtests of the WISC III performance IQ do assess visuospatial functioning and, therefore, our results of a lower performance IQ compared to the verbal IQ also confirm the findings of Ballantyne et al. [13].

The MRI findings in our study included enlarged ventricles and two incidental findings of mesial sclerosis of the hippocampus and developmental venous anomaly. The child with the mesial sclerosis of the hippocampus had an IQ of 71, and there may be an association of these two findings. The other structural MRI abnormalities were not associated with cognitive and motor dysfunction, possibly due, at least in part, to the small sample size. Importantly, neither MR spectroscopy nor diffusion tensor imaging revealed any abnormalities. Our results are in contrast to those reported in one study which detected cortical atrophy in the majority of patients. In that study, greater cortical atrophy was related to lower cognitive performance [39].

This is the first published study to assess MP in patients with cystinosis using a standardized assessment tool, i.e. the Zurich Neuromotor Assessment [27, 28], which has the advantage of providing a control group comprising healthy age-related Swiss children. Impaired MP may result in school problems related to fine motor difficulties, with substantial negative effect on academic performance. Gross motor difficulties may negatively affect peer interactions and subsequently profoundly impair feelings of well being and self-esteem. Few other studies have examined motor performance in this population. General muscular hypotonia has been a consistent finding in many children with chronic kidney diseases of various origins [40]. Muscular hypotonia can be associated with poorer motor perfor-

Table 3 Motor performance assessed with the Zurich Neuromotor Assessment

	Pure motor	Peg-board	Dynamic balance	Static balance	Movement quality
Median	−1.30*	−0.55*	−1.90	−1.10*	−1.05*
Range	−3.7 to 0.3	−2.3 to −0.1	−4.8 to 1.3	−4.1 to −0.3	−3.3 to −0.5

*$p<0.05$ (Wilcoxon signed ranks test compared to healthy controls)

Values are given as standard deviation scores (SDS)

Table 4 Quality of life assessed by means of the Child Quality of Life Questionnaire

Measure	Sample		Normative data [29]		*p* value
	Mean	Standard deviation	Mean	Standard deviation	
TACQOL-Child form					
Body	26.2	4.3	24.2	5.0	0.25
Motor	30.7	1.5	29.8	3.2	0.16
Autonomy	30.1	1.9	31.4	1.9	0.13
Cognition	26.7	4.9	28.5	3.9	0.37
Social	27.4	3.2	29.4	2.7	0.16
Positive Emotion	10.9	2.5	13.3	2.5	0.04*
Negative Emotion	12.4	1.8	11.6	2.7	0.33
TACQOL-Parent form					
Body	23	6.9	27.6	3.7	0.10
Motor	26.5	6.4	31	2.3	0.09
Autonomy	27*	4.3	31.4	1.6	0.05*
Cognition	21.5	7	29.2	3.7	0.04*
Social	26	4.8	30	2.3	0.05*
Positive Emotion	11.4	3	15	1.8	0.01*
Negative Emotion	11.0	2.5	11.7	2.3	0.46

TACQOL, Netherlands Organization for Applied Scientific Research Academical Medical Center (TNO–AZL) Child Quality of Life Questionnaire

*$p \leq 0.05$ compared with normative data (according to the *t* test)

mance, in particular with static balance tasks. One study that examined motor performance in young children using the Bayley Scales of Infant Development found that motor development was abnormal in 24% of children transplanted in early childhood [41]. Neurological co-morbidity was the most negative predictor of poor motor performance [41].

It has been suggested that mutations in the *CTNS* gene may influence brain development [42]. However, at least two studies have been unable to find a correspondence between intellectual development and cognitive functioning and the degree of observed cerebral atrophy [39, 43]. Patients not treated with cystine-depleting agents have been shown to suffer from ongoing cerebral atrophy [37]. In our small series of patients, the white matter myelination appeared to be normal on both the MRI and ^{1}H MRS scans.

One of the limitations of our study is the small number of patients, which limits the statistical power of our results. The impact of cysteamine dosage on the general outcome of our patients could not be assessed because white blood cell cystine levels were not routinely measured, and cysteamine dosage was maintained at 60 mg/kg per day. Furthermore, patients were examined independent of RTPL and, therefore, we could not analyse the effect of RTPL. In addition, different intelligence tests were used to assess intellectual performance. The results of the WISC-III and the K-ABC are somewhat difficult to compare because of different theoretical concepts. Assessing children at different ages may also underscore the true extent of the intellectual deficits since higher executive functions or specific learning disabilities may not be detected at young ages. Our results were compared to those of healthy control children and not to children with renal diseases unrelated to cystinosis. As such, we are unable to draw any conclusion on the specific neurocognitive profile of children with cystinosis in comparison to those with other renal disorders.

The self-reported QOL dimension of positive emotions of our small patient cohort was impaired compared with that of the healthy controls. For our patients with cystinosis, emotional disturbance seemed to be more important than physical complaints or motor functions; the parents also rated positive emotions as being significantly impaired, but in contrast to the assessment of their children, parents also rated autonomy,

Table 5 Psychosocial adjustment measured by means of the Child Behaviour Checklist

Measure	Sample		Normative data [31]		*p* value
	Mean	Standard deviation	Mean	Standard deviation	
CBCL total score	63	7.5	50	10	0.002*
CBCL internalizing score	65.4	10.6	50	10	0.005*
CBCL externalizing score	57.5	5.2	50	10	0.005*

*$p \leq 0.05$ compared with normative data (according to the *t* test)

CBCL, Child Behaviour Checklist

social and cognitive functions as being significantly impaired. This divergent rating of patients and parents, especially the tendency toward a more critical parental assessment, is noteworthy. This tendency has been observed in other chronically ill paediatric populations, such as in children with congenital heart disease after open-heart surgery [44], paediatric renal graft recipients [11] and children with relapsing diseases (steroid-sensitive nephrotic syndrome) [12]. This finding might reflect a shared variance between a mothers' psychological strain and the rating of her child's QOL [45]. Parents may have a different awareness of the impact of their child's chronic disease. Alternatively, affected patients may have scored their QOL too optimistically because of confusing factors (e.g. face-to-face interview, mechanisms of avoidance). We could not define any correlations between co-morbidity (e.g. hypothyroidism) and cysteamine treatment.

In contrast to other patients with chronic disorders, such as phenylketonuria or paediatric burn survivors [32, 33], patients with cystinosis showed both internalizing and externalizing disturbances. The patients' main complaints were directed against withdrawn, somatic complaints, anxiety, depression, attention problems and aggressive behaviour. These complaints may reflect the profound effect of the disorder and underlines the importance of these patients receiving adequate, supportive and comprehensive treatment. Our results were similar to those reported for children with relapsing steroid-sensitive nephrotic syndrome [12]. One explanation for this in steroid-sensitive nephrotic syndrome may be the adverse effects of steroids or the constant fear of imminent relapse by the parents [12]. In cystinosis, other reasons may be causal: patients need a life-long medical treatment, there is no curative treatment available to date, and, in particular, the long-term prognosis (e.g. diabetes mellitus, hypothyroidism, neurological and muscular complications) is poor despite life-long therapy [1].

It was not possible to define any determinants for QOL and PA in our cohort, as the number of patients was too small, although QOL seemed to improve after renal transplantation. However, our results do not include the progression of the multisystemic disorder, in particular the development of the brain and the muscular system. Further studies evaluating long-term outcome are required.

In patient D, who suffered from cystic fibrosis and cystinosis, results concerning QOL and PA were comparable with that of the other patients. This may indicate that the co-morbidity cystic fibrosis did not further impact on QOL and PA.

In summary, this observational study on children and adolescents with cystinosis suggests that intellectual performance, motor performance, health-related quality of life and psychosocial adjustment are impaired, thereby reflecting the extent of potential sequelae of this multisystemic disorder.

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